Remarks

I. The Office Action

Claims 28-37 are newly rejected under 35 U.S.C. §112, second paragraph, for the stated reason that the term "lambda type" is unclear. Claims 28-37 are also rejected under 35 U.S.C. §112, first paragraph, for the stated reason that there is no support for the term "lambda type" in the application as originally filed.

The rejection under 35 U.S.C. § 103(a) of claims 28-38, 43, 44, 47, and 48 for allegedly being obvious over U.S. Patent 4,792,447 ("the Uhr patent") in view of International Patent Publication WO 03/004056 ("the Raison publication"), Stavnezer et al., *J. Immunol., 137*, 3978-3982 (1986) ("the Stavnezer article") and Abe et al., *Am. J. Clin. Path., 100*, 67-74 (1993) ("the Abe article") is maintained. The examiner also maintains the rejection of claims 39-42, 45, and 46 under 35 U.S.C. § 103(a) for allegedly being obvious in view of the Uhr patent in view of the Raison publication and the Abe article, and in further view of U.S. Patent Publication No. US 2005/0255532 ("the Ruben publication").

Reconsideration of the rejections is respectfully requested.

II. The Amendments to the Claims

Claims 28, 33 and 40 have been amended to state that the lymphoid target cells of the recited methods are "lymphoid cells that express free lambda light chain" (referred to as "LMA" in the present application). The amendment is supported by the specification at, for example, page 1, lines 6-8. No new matter is introduced by the amendments.

III. There is Written Description and Clarity

The Examiner asserts there is no support in the specification for the term "lambda type" as used in claims 28, 33 and 40. In addition, the Examiner contends that the term "lambda type" has no known meaning in the art.

In order to further prosecution of the application, but without acquiescing to the rejections, claims 28, 33 and 40 are presently amended to refer to "lymphoid cells expressing surface free lambda light chain".

The rejections under Section 112 should therefore be withdrawn.

IV. The Rejections under Section 103(a) Should Be Withdrawn

The Examiner maintains that claims 28-38, 43, 44, 47 and 48 are obvious in light of the Uhr patent when combined with the Raison publication, the Stavnezer article and the Abe article. The Examiner argues "it would have been expected by a routineer that lambda light chain expressing myeloma cells would have been found which express free lambda light chain" (emphasis added). Based on the same reasoning the Examiner also maintains the rejection of claims 39-42, 45, and 46.

In particular, while the Examiner recognizes that the Uhr patent does not teach a method of treating a B-cell disorder by administering an antibody that binds free lambda light chain on the cell surface, the examiner argues because there are only two known light chain alleles (kappa and lambda), because the Stavnezer article allegedly teaches that free lambda light chain can be expressed on the surface of a leukemia tumor cell, and because the Abe article discloses antibodies which bind free lambda light chain, it would have been expected as a matter of routine that myeloma cells expressing free lambda light chain on the cell surface would have been found.

With a previous response, Applicants submitted the "Declaration by Cameron Jennings, PhD", a person skilled in the art, setting out various structural, functional and expression differences between kappa and lambda light chains. As a result of these differences, Dr Jennings declared that a skilled person could not have predicted that free lambda light chain would be associated with the membrane of tumor B-cells.

The Examiner has dismissed the declaration, in view of the decision in *Ex parte Erlich*, because it cites some post-filing art. Applicants respectfully submit that the declaration by Dr. Jennings cites scientific articles from before the priority date of the invention as evidence that the structure and function (including binding characteristics) of kappa and lambda light chains were known to be different in the art. For example, Kabat *et al.* (1975), Zimmer *et al.* (1990), Khurana *et al.* (2001), Solomon and Weiss (1995) and Dariavach *et al.* (1987) are cited as teaching the fundamental differences in structure of the kappa and lambda light chains. In addition, Graille *et al.* (2001) teaches that the ability of kappa and lambda light chain to bind a given protein is different (*i.e.*, while kappa light chain variable region binds *P. magnus* protein L, lambda light chain does not). The Examiner has not addressed these documents cited in the declaration.

The post-filing art that was cited in the declaration merely confirmed the already known differences in structure and function between kappa and lambda light chains. Thus, the factual scenario in *Ex parte Erlich* is different from the present circumstances. In *Ex parte Erlich*, the applicant relied on an earlier published document (1975) to support an argument for unpredictability in the art, whereas a document published just prior to the invention removed this unpredictability. As discussed in a previous response, in the present case there is no intervening prior art cited by the Examiner which removes the unpredictability in light of the earlier published art (Kabat *et al.* (1975), Zimmer *et al.* (1990), Khurana *et al.* (2001), Solomon and Weiss (1995), Dariavach *et al.* (1987), and Graille *et al.* (2001). That the declaration of Dr Jennings also cites later confirmatory art is irrelevant in view of the decision in *Ex parte Erlich*. Indeed, there is nothing in *Ex parte Erlich* to support the Examiner's position that later published documents in the declaration should mean the documents published before the priority date could be dismissed from consideration, yet it appears this is what the Examiner has done.

The Examiner states that comments made in relation to documents published after the effective filing date of the application "ignore the fact that surface bound kappa light was already known in the art." Applicants respectfully disagree. The declaration cites several documents published before the filing date of the invention that demonstrate it was widely known in the art that there are significant structural and function differences between kappa and lambda light chain. The declaration was made with the knowledge that kappa light chain is present on the surface of kappa myeloma cells. The very point of the declaration is to demonstrate that, despite the knowledge of surface bound kappa light chain on myeloma cells, it could not have been predicted by a routineer that free lambda light would be expressed on the surface of lambda myeloma cells.

In this regard, Graille *et al.* (2001) was cited as evidence of this unpredictability in the art at the time the invention was made. Graille *et al.* teach that while kappa light chains bind Protein L, which is used in the art for the purification of monoclonal antibodies, lambda light chains do not.

The Examiner further states that "both sets of light chain are structurally similar in the ability to form dimers with Ig heavy chain". While it is not disputed that kappa and lambda light chains both form dimers with heavy chain via disulfide bonds, the declaration by Dr Jennings demonstrates that it was known in the art that the kappa and lambda light chains are

structurally dissimilar, contrary to the Examiner's assertion. Regardless, the claims recite antibodies that bind lambda light chain in the absence of heavy chain. The declaration sets out that in the absence of heavy chain, it could not be predicted that kappa and lambda light chains could associate with similar molecules on the cell surface.

In addition, the Examiner states "in view of the ability of both types of light chains to associate with heavy chain it would be reasonable to conclude that kappa and lambda light chains would have a similar ability to associate with molecules other than Ig heavy chain." Applicants respectfully submit that the documents cited in the declaration by Dr. Jennings refute the Examiner's opinion. Indeed, Graille *et al.* clearly demonstrate that it could not be predicted that lambda light chain would bind a polypeptide to which kappa light chain was known to bind.

Furthermore, there is nothing in the prior art cited by the Examiner that teaches which molecule(s) kappa light chain associates with on the surface of kappa myeloma cells, or that such molecules would be present on the surface of lambda myeloma cells. We respectfully submit that even if the prior art taught the molecule(s) to which kappa light chain associates with on the surface of kappa myeloma cells, and even if it was known that the molecule(s) were present on lambda myeloma cells, in light of the declaration by Dr Jennings and in particular in view of Graille *et al.* (2001), it could not have been predicted at the time the invention was made that lambda light chain would associate with the molecule(s) on the surface of lambda myeloma cells.

Thus, the declaration by Dr Jennings establishes that the person skilled in the art, in view of the Raison publication, would not have expected as a matter of routine at the time the invention was made that free lambda light chain would be found on the membrane of lambda myeloma cells.

While still relying on the foregoing points and again in the interest of furthering prosecution, Applicants submit herewith a revised declaration of Dr. Jennings executed February 3, 2012 which only refers to documents published before the priority date to which the present application is entitled.

With regard to the Stavnezer article, Applicants respectfully disagree with the Examiner's characterization. The Stavnezer article relates to experiments with the HL-60 cell line, which is a myeloid progenitor cell. In contrast, the present invention is directed to

cells of the lymphoid lineage. A diagram demonstrating the difference between the cell lineages is submitted herewith.

The Examiner notes that the Stavnezer article discloses that the HL-60 cell line has B-cell lymphoid characteristics. While suggesting the expression of lambda light chain on the HL-60 cells, however, the Stavnezer article does not suggest that HL-60 cells could differentiate along the lymphoid lineage. Rather, the article teaches that when inducing the cells to differentiate by treatment with TPA, the cells differentiated down the myeloid pathway. The authors state "treatment of HL-60 cells with TPA induces macrophage differentiation, and treatment with retinoic acid or DMSO induces myeloid cell markers; however, no agent has yet been reported to induce additional lymphoid differentiation of these cells" (emphasis added). Furthermore, the Stavnezer article demonstrates that TPA-treated cells lose the surface lambda chains and lambda RNA expression (see page 3981, left hand column, second paragraph). Thus, the cited document clearly teaches that upon differentiation, HL-60 cells differentiate along the myeloid lineage and lose expression of the purported lambda light chain.

In addition, the Stavnezer article authors question their own finding of lambda light chain on the surface of the HL-60 myeloid progenitor cells. For example, they test for immunoglobulin light chain mRNA and immunoglobulin gene rearrangements that would be expected if lambda light chain was expressed in the cells (see the end of page 3979 to the right hand column of page 3980). While some RNA was reported to be detected, no rearranged genes were detected which is a conflicting result. The authors themselves are unable to explain their results with any certainty as shown in the third paragraph of page 3981. Still unable to explain their results, the authors continue in the fourth paragraph of page 3981 by stating "it is possible that the λ chains detected were in the process of being passively released or actively secreted from the HL-60 cells" rather than being associated with the cell surface. Thus, the Stavnezer article actually teaches away from targeting lambda light chain in view of the fact the authors suggest that it is not surface expressed, but rather secreted from the cell.

Finally, as Stavnezer *et al.* was published 18 years before the priority date of the present application, Applicants respectfully submit that it does not represent the state of the art at the time the invention was made. In this regard, there is intervening prior art published between the Stavnezer article and the priority date that teaches that HL-60 cells do not

express lambda light chain. Thus, while the Stavnezer article reports the "finding" of lambda light chain on the surface of myeloid progenitor cells while questioning the veracity of its own results, Tepper and Studzinski, *Cancer Res., 52*; 8834-3390 (1992) (submitted herewith) teaches that HL-60 cells do not express lambda light chain constant region genes.

In the Tepper and Studzinski article, the authors investigate the effect of teniposide treatment on irreversible DNA degradation in HL-60 cells and whether or not DNA degradation is gene specific. To test whether the effect is gene specific, the authors analyse DNA from treated HL-60 cells. While the genes for 18s rRNA and glucose-6-phosphate dehydrogenase were chosen as representatives of constitutively expressed genes, λ light chain constant region genes were chosen because they are "transcriptionally inactive" in HL-60 cells (see Abstract and page 3386, second column, last paragraph). Indeed, the authors state "...these genes are never expressed in the myelomonocytic HL-60 cells" (emphasis added). Thus, the suggestion of surface lambda light chain on HL-60 cells by the Stavnezer article in 1986 was not the view of those in the art by 1992 (before the priority date of this application). Moreover, the view that HL-60 cells do not express lambda light chain continued as is evidenced by Figure 2 and Table 3 of Yao *et al., Clinical Chemistry, 48*(8): 1344-1351 (2002) (submitted herewith) which published even ten years later than the Tepper and Studzinski article, close to the 2004 priority date of the application.

Thus, in view of *Ex parte Erlich* which states that predictability is determined at the time the invention was made, and in view of the clear teaching of Tepper and Studinski (1992) and Yao *et al.* (2002), it would not have been predicted by a routineer at the priority date of the invention that myeloid cells (HL-60 cells), let alone cells of a different lineage (*i.e.*, lymphoid cells), would have expressed surface lambda light chain.

In view of the foregoing, Applicants respectfully submit the subject matter of the pending claims is not obvious in light of the combinations of the cited prior art and that the Section 103 rejections should be withdrawn. Neither of the combinations of cited documents suggest the concept of targeting LMA (free lambda light chain) on the surface of lambda-type lymphoid cells to treat B cell disorders.

Conclusion

Applicants submit the claims are in good and proper form for allowance, and the examiner is respectfully requested to pass this application to issue.

This paper is accompanied by petition for a three-month extension of time with the required fee. The commissioner is authorized to charge any additional fees due in connection with this filing to Marshall, Gerstein and Borun, LLP deposit account number 13-2855, under order no. 29729/38914.

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